

December 29, 1951

Dear Dr. Work:

I have taken note of your postcard asking for publications on the mechanism of action of antibiotics for your forthcoming review. If nothing has been sent, it is only because this is a subject with which I am only obliquely concerned.

I am writing to enquire whether, in the course of collecting the material for your review, you have encountered any discussion of Oginsky, Smith, and Umbreit's paper (J. Bact. 1948) on the metabolism of streptomycin-resistant mutants of E. coli. One of my colleagues was impressed by the overt similarity of the reported characteristics of such mutants, with those of the "petites" mutants of yeast, induced by acriflavine as worked on by Ephrussi. The most impressive statement was that the resistant mutants' growth was not benefitted by aeration, whereas the normal strains can be improved to the extent of tenfold over a 24-hour period. ~~XXXXXXXXXX~~ ~~XXXXXXXXXX~~ It was thought that the non-aerobic metabolism might be a direct modification induced by streptomycin, but which could only come to light in a resistant mutant that survived exposure to the antibiotic. This would be comparable to the effect of acriflavine which is presumably based on the removal or inactivation of certain "self-reproducing" chondriosome-like elements of the cytoplasm in yeast. Mrs. Lederberg and I had just developed a method for indirect selection of resistant mutants, which permits the isolation of rare mutants without directly exposing the cells to a selective agent. Since we had, in this way, obtained streptomycin-resistant mutants the hypothesis of a direct action of the streptomycin could be tested.

Unfortunately, none of our many resistant mutants in a variety of strains showed the non-aerobic growth behavior. The same held for subcultures of the E. coli strains originally used by Oginsky et al., and some correspondence I have had with her indicates that they have had some difficulty in reproducing this particular feature of their experiments. This raises the question whether the non-aerobic behavior of their original mutants was directly connected with their streptomycin-resistance. A few other people in the U.S. have indicated an experience like my own; I wondered whether you might not have gleaned some published or unpublished comment on it.

The indirect selection method is quite straightforward, but I have not the space to recount it here: a paper on it is scheduled for the Jan. '52 Jour. Bact. Its conclusions are worth emphasizing, however, especially to a prospective review-writer. Streptomycin-resistant mutants can be obtained from cell lineages never exposed to streptomycin, or any other unusual conditions. The same method is applicable to any mutation that can be selected on agar.

in pure
culture

Yours sincerely,

Joshua Lederberg
Associate Professor of Genetics